Citation:

De Lorgeril M, Salen P, Martin JL, Monjaud I, Delaye J, Mamelle N. Mediterranean Diet, traditional risk factors, and the rate of cardiovascular complications after myocardial infarction, final report of the Lyon Diet Heart Study. *Circulation*. 1999; 99: 779-785.

Worksheet created prior to Spring 2004 using earlier ADA research analysis template.

PubMed ID: 9989963

Study Design:

Randomized controlled trial.

Class:

A - Click here for explanation of classification scheme.

Research Design and Implementation Rating:

NEUTRAL: See Research Design and Implementation Criteria Checklist below.

Research Purpose:

Present results of an extended follow-up of patients involved in the Lyon Diet Heart Study (comparing the Mediterranean Diet and the regular therapeutic diet recommended by physicians for cardiovascular disease) regarding the relationships of dietary patterns and traditional risk factors with recurrence of cardiovascular complications.

Inclusion Criteria:

- Inclusion criteria for Lyon Diet Heart Study:
  - Survived first myocardial infarction (MI)
  - Less than 70 years of age
  - Clinically stable
  - Able to participate in dietary trial
  - Agreed to participate in cohort study with a follow-up of five years
- Inclusion in this study: Agreed to come to Research Unit for final visit.

Exclusion Criteria:

Medical or social condition that would limit their ability to participate in a dietary trial.

Description of Study Protocol:

Recruitment

During patient's hospital stay, they were asked to participate in a cohort study with a follow-up of five years. They were not fully informed about the design of the study, especially regarding the comparison of the two diets.

Design

Randomized secondary prevention trial, control and experimental groups, blinded evaluation of raw data obtained from hospital files and, for patients who had died, from civil status office of the patient's birthplace.

Blinding Used

Researchers conducted a blind evaluation of raw data. Participants were not fully informed of the study design, especially the comparison of the two diets.

Intervention

Participants were randomized between March 1988 and March 1992 into experimental and control groups. Participants in the experimental group were asked to comply with a Mediterranean-type diet and had to sign a second consent form. Participants in the control group received no dietary advice from the investigators but nonetheless were advised to follow a prudent diet by their attending physicians. The diets have been described in detail in other research articles. Because of statistically significant results found during an intermediate analysis, the decision was made to stop the trial. All patients were invited to come to the Research Unit for a final visit, during which they were fully informed about the main results of the trial. Hence, given the delay after the clinical status of the two groups in March, 1993, the decision to invite the patients to a new assessment and the time needed to see each patient, an additional follow-up of approximately 19 months was available in the two groups to perform the final analyses. This offered the opportunity to evaluate the long-term (mean, four years) effect of the diet tested in the trial and whether the patients continued to comply with it.

The dietary instructions were detailed and customized to each patient, and a dietary survey at each visit allowed researchers to check for adhesion and compliance to the experimental diet. In addition, plasma fatty acids were analyzed (gas-liquid chromatography) in the two groups as described and used as objective biomarkers.

Statistical Analysis

Analyses were done on the intention-to-treat principle. Event-free survival for myocardial infarction, cardiovascular death and three composite outcomes (COs) were estimated by the Kaplan-Meier method. The censoring date was the date of the earliest event of the end of follow-up. The Cox proportional-hazards model was used to calculate the risk ratios and to quantify the associations between each traditional risk factor and the different COs.

Data Collection Summary:

Timing of Measurements

Clinical data was frozen after a minimum of follow-up of one year for each patient. The study was stopped after June, 1994 and participants were invited to hear results of the trial and receive a new assessment. Only clinical events requiring hospital admission were considered. A dietary survey at each visit allowed researchers to check for adhesion and compliance to experimental diet.

Dependent Variables

- *Variable 1, Composite Outcome 1 (CO1):* Myocardial infarction plus cardiovascular death

(obtained from hospital files or civil status office of patient's birthplace if patient had died)
- *Variable 2, Composite Outcome 2 (CO2):* Myocardial infarction, cardiovascular death and major secondary events including episodes of unstable angina, episodes of overt heart failure, stroke or pulmonary or peripheral embolism (obtained from hospital files or civil status office of patient's birthplace if patient had died)
- *Variable 3, Composite Outcome 3 (CO3):* Myocardial infarction, cardiovascular death and major secondary events including episodes of unstable angina, episodes of overt heart failure, stroke or pulmonary or peripheral embolism plus minor events requiring hospital admission, including recurrent stable angina, postangioplasty restenosis, surgical or medical myocardial revascularization and thrombophlebitis (obtained from hospital files or civil status office of patient's birthplace if patient had died)
- *Variable 4:* Event-free survival after myocardial infarction (obtained from hospital files or civil status office of patient's birthplace if patient had died)
- *Variable 5:* Cardiovascular death (obtained from civil status office of patient's birthplace).

Independent Variables

Dietary intake (measured by dietary survey at each visit).

Control Variables

- Plasma fatty acids used as objective biomarkers (analyzed using gas-liquid chromatography)
- Medications recorded two months after randomization (considered in a separate analysis).

Description of Actual Data Sample:

- *Initial N:* Unclear, possibly reported elsewhere
- *Attrition (final N):* 423 [Among the patients who did not come for a final visit (15 control and 19 experimental), the vital status was unknown for four patients (three control and one experimental)]. The great majority (93.4% of control and 92.4% of experimental subjects) of patients still alive and not censored at the time of the final visit in the two groups agreed to come to the Research Unit.

Anthropometrics

Main Risk Factors and Selected Biological Parameters Recorded on the Final Visit [Values Are Mean (SD)]

	Control	Experimental
	(N=204)	(N=219)
Body mass index, kg/m^2	26.9 (3.4)	26.3 (3.7)
Systolic blood pressure, mm Hg	128 (16)	128 (17)
Diastolic blood pressure, mm Hg	79 (10)	78 (11)
Total cholesterol, mmol per L	6.18 (1.04)	6.20 (1.06)
Triglycerides, mmol per L	1.75 (0.83)	1.94 (0.85)
HDL-cholesterol, mmol per L	1.28 (0.34)	1.29 (0.34)
LDL-cholesterol, mmol per L	4.23 (0.98)	4.17 (0.93)
Lipoprotein (a), g per L	0.35 (0.49)	0.33 (0.35)

Albumin, g per L	47.10 (2.88)	47.28 (3.07)
Glycated hemoglobin, %	4.61 (1.23)	4.66 (1.52)
Creatinine, µmol per L	116 (20)	115 (21)
Uric acid, µmol per L	348 (81)	338 (87)
Leukocyte count, x109 per L	6.00 (1.69)	5.99 (1.68)
Current smokers, %	17.9	18.3
Medication, %		
Anticoagulant agents	16.1	11.4
Antiplatelet agents	69.7	75.8
B-Blocking agents	47.3	47.5
Calcium channel blockers	28.3	25.6
ACE inhibitors	17.4	18.3
Lipid-lowering drugs	34.0	26.5

Summary of Results:

Mean follow-up for survival was 44.9 months in the control group and 46.7 months in the experimental group.

Multivariate Proportional: Hazards Analyses Associating Selected Traditional Risk Factors

	Conditional Risk Ratios and 95% CIs		
Variables	**CO1**	**CO2**	**CO3**
Diet group (Mediterranean vs. control)	0.23 (0.11-0.48)	0.30 (0.18-0.51)	0.51 (0.35-0.73)
Age, years	0.98 (0.95-1.02)	1.00 (0.98-1.03)	1.00 (0.98-1.02)
Sex, male vs. female		0.60 (0.18-2.01)	0.87 (0.39-1.94)
Smoking, yes or no	1.50 (0.67-3.37)	1.52 (0.81-2.88)	0.98 (0.57-1.69)
Total cholesterol, mmol per L	1.31 (1.05-1.65)*	1.31 (1.10-1.57)*	1.22 (1.06-1.40)*
Systolic blood pressure, mm Hg	1.01 (0.98-1.03)	1.02 (0.99-1.04)	1.00 (0.99-1.01)
Leukocyte count, x109 per L	1.48 (1.06-2.07)	1.49 (1.16-1.90)	1.07 (0.87-1.32)
Aspirin use, yes or no	0.59 (0.35-1.01)	0.63 (0.41-0.94)	0.82 (0.59-1.14)

*Significant associations (P<0.05).

Among the medications used, only aspirin was significantly (and inversely) associated with the outcomes and was then included in the multivariate analyses. A threshold effect was observed with leukocyte count (quartile analyses), with a markedly increased risk when the count was more than 9x109 per L. Thus, leukocyte count was used as a categorical variable, whereas total cholesterol and blood pressure (no J-shaped curve) were used as continuous variables in further analyses.

Univariate Associations Between Traditional Risk Factors and the Three COs

	Conditional Risk Ratios and 95% CIs		
Variables	**CO1**	**CO2**	**CO3**
Diet group (Mediterranean vs. control)	0.23 (0.11-0.48)	0.30 (0.18-0.51)	0.51 (0.35-0.73)

Age, years	0.98 (0.95-1.02)	1.00 (0.98-1.03)	1.00 (0.98-1.02)
Sex, male vs. female		0.60 (0.18-2.01)	0.87 (0.39-1.94)
Smoking, yes or no	1.50 (0.67-3.37)	1.52 (0.81-2.88)	0.98 (0.57-1.69)
Total cholesterol, mmol per L	1.31 (1.05-1.65)*	1.31 (1.10-1.57)*	1.22 (1.06-1.40)*
HDL-cholesterol, mmol per L	0.59 (0.17-2.10)	0.42 (0.16-1.12)	0.50 (0.24-1.04)
Systolic blood pressure, mm Hg	1.01 (0.98-1.03)	1.02 (0.99-1.04)	1.00 (0.99-1.01)
Diastolic blood pressure, mm Hg	1.01 (0.97-1.05)	0.99 (096-1.02)	1.01 (0.99-1.03)
Blood glucose, mmol per L	1.11 (0.89-1.36)	1.03 (0.89-1.18)	0.96 (0.84-1.09)
Serum albumin, g per L	0.97 (0.89-1.06)	0.97 (0.91-1.04)	1.00 (0.95-1.05)
Leukocyte count, x109 per L	1.48 (1.06-2.07)	1.49 (1.16-1.90)	1.07 (0.87-1.32)
Neutrophil count, x109 per L	0.81 (0.53-1.23)	0.76 (0.65-1.04)	1.05 (0.80-1.38)

*Significant associations (P<0.05).

Risk ratios are calculated with the Cox proportional-hazards model.

With regard to any association between the plasma concentration of major fatty acids and recurrence, only 18:3 (omega-3) tended to be inversely associated with recurrence (P=0.11 and P=0.16, respectively, vs. CO1).

When the plasma fatty acid concentrations were entered into the Cox proportional hazards model, 18.3 (omega-3) was the only fatty acid significantly associated with CO1 (risk ratio, 0.20; 95% CIs, 0.05 to 0.84 after adjustment for age, sex, smoking, total cholesterol, blood pressure, leukocyte count and aspirin use). With regard to the effect of 18.3 (omega-3) on C02 and CO3, the associations were borderline nonsignificant (P=0.08 and P=0.12).

Author Conclusion:

Including a total of 275 events recorded during a mean follow-up of 46 months, this report shows that longer follow-up and inclusion of more events in the analyses do not substantially alter the picture in the Lyon Study and confirm the results of the intermediate analysis. Also, the influence of the risk factors on prognosis was similar to that reported in other low-risk populations, indicating that a low-fat Mediterranean diet does not qualitatively alter the usual relationships between the risk factors and recurrence rate.

Reviewer Comments:

The Lyon Diet Heart Study had been previously published; not all of the details of the study were included in this paper.

Research Design and Implementation Criteria Checklist: Primary Research

Relevance Questions

1.	Would implementing the studied intervention or procedure (if found successful) result in improved outcomes for the patients/clients/population group? (Not Applicable for some epidemiological studies)	Yes
2.	Did the authors study an outcome (dependent variable) or topic that the patients/clients/population group would care about?	Yes
3.	Is the focus of the intervention or procedure (independent variable) or topic of study a common issue of concern to nutrition or dietetics practice?	Yes
4.	Is the intervention or procedure feasible? (NA for some epidemiological studies)	Yes

Validity Questions

1.	**Was the research question clearly stated?**	Yes
1.1.	Was (were) the specific intervention(s) or procedure(s) [independent variable(s)] identified?	Yes
1.2.	Was (were) the outcome(s) [dependent variable(s)] clearly indicated?	Yes
1.3.	Were the target population and setting specified?	No
2.	**Was the selection of study subjects/patients free from bias?**	Yes
2.1.	Were inclusion/exclusion criteria specified (e.g., risk, point in disease progression, diagnostic or prognosis criteria), and with sufficient detail and without omitting criteria critical to the study?	Yes
2.2.	Were criteria applied equally to all study groups?	Yes
2.3.	Were health, demographics, and other characteristics of subjects described?	Yes
2.4.	Were the subjects/patients a representative sample of the relevant population?	Yes
3.	**Were study groups comparable?**	Yes
3.1.	Was the method of assigning subjects/patients to groups described and unbiased? (Method of randomization identified if RCT)	Yes
3.2.	Were distribution of disease status, prognostic factors, and other factors (e.g., demographics) similar across study groups at baseline?	Yes
3.3.	Were concurrent controls used? (Concurrent preferred over historical controls.)	Yes
3.4.	If cohort study or cross-sectional study, were groups comparable on important confounding factors and/or were preexisting differences accounted for by using appropriate adjustments in statistical analysis?	N/A

3.5.	If case control or cross-sectional study, were potential confounding factors comparable for cases and controls? (If case series or trial with subjects serving as own control, this criterion is not applicable. Criterion may not be applicable in some cross-sectional studies.)	N/A
3.6.	If diagnostic test, was there an independent blind comparison with an appropriate reference standard (e.g., "gold standard")?	N/A
4.	**Was method of handling withdrawals described?**	No
4.1.	Were follow-up methods described and the same for all groups?	Yes
4.2.	Was the number, characteristics of withdrawals (i.e., dropouts, lost to follow up, attrition rate) and/or response rate (cross-sectional studies) described for each group? (Follow up goal for a strong study is 80%.)	No
4.3.	Were all enrolled subjects/patients (in the original sample) accounted for?	No
4.4.	Were reasons for withdrawals similar across groups?	???
4.5.	If diagnostic test, was decision to perform reference test not dependent on results of test under study?	N/A
5.	**Was blinding used to prevent introduction of bias?**	Yes
5.1.	In intervention study, were subjects, clinicians/practitioners, and investigators blinded to treatment group, as appropriate?	Yes
5.2.	Were data collectors blinded for outcomes assessment? (If outcome is measured using an objective test, such as a lab value, this criterion is assumed to be met.)	Yes
5.3.	In cohort study or cross-sectional study, were measurements of outcomes and risk factors blinded?	N/A
5.4.	In case control study, was case definition explicit and case ascertainment not influenced by exposure status?	N/A
5.5.	In diagnostic study, were test results blinded to patient history and other test results?	N/A
6.	**Were intervention/therapeutic regimens/exposure factor or procedure and any comparison(s) described in detail? Were interveningfactors described?**	No
6.1.	In RCT or other intervention trial, were protocols described for all regimens studied?	No
6.2.	In observational study, were interventions, study settings, and clinicians/provider described?	N/A
6.3.	Was the intensity and duration of the intervention or exposure factor sufficient to produce a meaningful effect?	Yes
6.4.	Was the amount of exposure and, if relevant, subject/patient compliance measured?	Yes

6.5.	Were co-interventions (e.g., ancillary treatments, other therapies) described?	???
6.6.	Were extra or unplanned treatments described?	???
6.7.	Was the information for 6.4, 6.5, and 6.6 assessed the same way for all groups?	???
6.8.	In diagnostic study, were details of test administration and replication sufficient?	N/A
7.	**Were outcomes clearly defined and the measurements valid and reliable?**	Yes
7.1.	Were primary and secondary endpoints described and relevant to the question?	Yes
7.2.	Were nutrition measures appropriate to question and outcomes of concern?	Yes
7.3.	Was the period of follow-up long enough for important outcome(s) to occur?	Yes
7.4.	Were the observations and measurements based on standard, valid, and reliable data collection instruments/tests/procedures?	Yes
7.5.	Was the measurement of effect at an appropriate level of precision?	Yes
7.6.	Were other factors accounted for (measured) that could affect outcomes?	Yes
7.7.	Were the measurements conducted consistently across groups?	Yes
8.	**Was the statistical analysis appropriate for the study design and type of outcome indicators?**	Yes
8.1.	Were statistical analyses adequately described and the results reported appropriately?	Yes
8.2.	Were correct statistical tests used and assumptions of test not violated?	Yes
8.3.	Were statistics reported with levels of significance and/or confidence intervals?	Yes
8.4.	Was "intent to treat" analysis of outcomes done (and as appropriate, was there an analysis of outcomes for those maximally exposed or a dose-response analysis)?	Yes
8.5.	Were adequate adjustments made for effects of confounding factors that might have affected the outcomes (e.g., multivariate analyses)?	Yes
8.6.	Was clinical significance as well as statistical significance reported?	Yes
8.7.	If negative findings, was a power calculation reported to address type 2 error?	???
9.	**Are conclusions supported by results with biases and limitations taken into consideration?**	Yes
9.1.	Is there a discussion of findings?	Yes

	9.2.	Are biases and study limitations identified and discussed?	Yes
10.	**Is bias due to study's funding or sponsorship unlikely?**		Yes
	10.1.	Were sources of funding and investigators' affiliations described?	Yes
	10.2.	Was the study free from apparent conflict of interest?	Yes